REMARKS

Reconsideration of the present application is requested in view of the foregoing amendments and the following remarks.

I. Examiner Interview Summary

The Applicants thank Examiner Goldberg for participating in a telephonic interview with the Applicants' representative, M. Scott McBride, on February 26, 2008. During the interview, the participants discussed the outstanding rejection of the claims under 35 U.S.C. § 103(a) for obviousness and under 35 U.S.C. § 112, first paragraph for lack of enablement.

Regarding the rejection for obviousness, the Applicants proposed amending the claims to include detecting methylation in DAPK in view of the Examiner having previously determined that the prior art does not appear to teach detecting DAPK to characterize breast cancer. Regarding the rejection for lack of enablement, the Applicants proposed submitting an inventor's Declaration under 37 C.F.R. § 1.132 by inventor Dr. Victor V. Levenson that would endeavor to demonstrate that the claimed methods can be performed for diagnosing breast cancer in a patient. In particular, the Declaration would endeavor to demonstrate that DAPK could be used as part of a panel of genes for diagnosing breast cancer.

The participants also discussed the restriction requirement issued in the Office Action dated August 10, 2007, wherein the Examiner required that Applicants elect a single combination of genes including DAPK with respect to then pending claims 3-14. The Applicants asked that the Examiner consider withdrawing the restriction requirement if the proposed claim amendments and inventor's Declaration placed the broadest claims in condition for allowance. The Examiner agreed to review the claim amendments and inventor's Declaration and to make a determination afterwards in regard to the restriction requirement.

II. Amendments to the Specification

The Title has been amended to reflect the subject matter of the amended claims. This amendment does not introduce new matter and entry thereof is requested.

III. Amendments to the Claims

Prior to entry of the foregoing amendment, claims 1-14, 23-31, and 33 were pending.

Claims 6-11, 29, and 30 are requested to be cancelled without disclaimer or prejudice to further prosecution on the merits.

Claims 1-5, 13, 14, 24, and 33 currently are amended.

Claim 1 is amended to correct typographical and grammatical errors and to clarify the claimed subject matter. In particular, claim 1 is amended to recite a method "for diagnosing breast cancer." The claimed method includes contacting a plasma sample with at least five different pairs of gene specific primers, wherein the gene specific primers are configured to hybridize to genomic DNA and amplify five different promoters from at least five different genes. Claim 1 also has been amended to recite the phrase "including DAPK" with respect to these different genes. Claim 1 also has been amended to recite the phrase "thereby diagnosing breast cancer in the subject." These amendments do not introduce new matter.

Claim 2 is amended to correct typographical and grammatical errors. These amendments do not introduce new matter.

Claim 3 has been amended to correct typographical and grammatical errors and to clarify the claimed subject matter. In particular, claim 3 is amended to recite a method of characterizing "breast cancer in a subject." Claim 3 also is amended to recite "providing a plasma sample." The claimed method includes detecting the presence or absence of DNA methylation in a plurality of different genes including DAPK, similarly as recited in claim 1. Claim 3 also has been amended to recite the

phrase "thereby characterizing breast cancer in the subject." These amendments do not introduce new matter.

Claim 4 has been amended to recite the phrase "wherein the plurality of different genes include a gene selected from the group consisting of FAS, MCT1, p16, PAX5, THBS, TRANCE, and VHL." Support for the genes in this list is provided in the Specification, for example, at Figures 2 and 3. This amendment does not introduce new matter.

Claim 5 has been amended to recite the phrase "wherein said characterizing breast cancer comprises diagnosing breast cancer." This amendment does not introduce new matter.

Claims 13 and 14 are amended to correct typographical and grammatical errors. These amendments do not introduce new matter.

Claim 24 has been amended to recite the phrase "wherein said gene specific primers are configured to hybridize to said genomic DNA and amplify five different promoters from at least five different genes including DAPK and a gene selected from a group consisting of FAS, MCT1, p16, PAX5, THBS, TRANCE, and VHL." Support for the genes in this list is provided in the Specification, for example, at Figures 2 and 3. This amendment does not introduce new matter.

Claim 25 is amended to correct a typographical error. This amendment does not introduce new matter.

Claim 33 is amended to correct typographical and grammatical errors and to clarify the claimed subject matter. In particular, claim 33 is amended to recite a method "for diagnosing breast cancer." The claimed method includes contacting an experimental sample with gene specific primers for a plurality of different genes including DAPK, similarly as recited in claims 1 and 3. Claim 33 also has been amended to recite the phrase "thereby diagnosing breast cancer in the subject." These amendments do not introduce new matter.

Claim 34 is requested to be added. New claim 34 recites the phrase "wherein the plurality of different genes include a gene selected from a group consisting of FAS, MCT1, p16, PAX5, THBS,

TRANCE, and VHL." Support for the genes in this list is provided in the Specification, for example, at Figures 2 and 3. Claim 34 does not introduce new matter.

Because the claim amendments do not introduce new matter and otherwise are proper, entry thereof is requested. After entry of the foregoing amendments, claims 1-5, 12-14, 24-28, 31, 33, and 34 are pending.

IV. Summary of Claimed Subject Matter

The claimed subject matter relates to methods for diagnosing or characterizing breast cancer in a subject. The methods include detecting the presence or absence of methylation in a plurality of genes including DAPK.

V. Claim Rejections - 35 U.S.C. § 103(a)

Claims 1, 2, 23-29, 31 and 33 are rejected under 35 U.S.C. § 103(a) over Kusui *et al.* (Biochemical and Biophysical Research Communications, Vol. 289, pages 681-686, 2001 (hereinafter "Kusui *et al.*") further in view of additional cited references. The Applicants respectfully traverse the rejection in view of the foregoing amendments and for the following reasons.

Claims 29 and 30 have been cancelled, obviating the rejection.

Claims 1 and 33, from which the remaining rejected claims depend, have been amended to recite methods for diagnosing or characterizing breast cancer in a subject that include detecting the presence or absence of methylation in a plurality of genes including DAPK. None of the cited references teach or suggest the methods as claimed.

Furthermore, the Office Action dated January 16, 2007 found that then pending claims 3-14 were allowable, stating:

> The prior art does not appear to teach detecting DAPK to characterize breast cancer. Thus, the ordinary artisan would not have been

> motivated to analyzed [sic] DAPK with the other known breast cancer associated genes.

(*See* Office Action dated January 16, 2007, at page 2, No. 3.)

For these reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) over Kusui *et al.* further in view of the additional cited references are requested.

VI. Claim Rejections - 35 U.S.C. § 112, first paragraph, "lack of enablement"

Claims 3-14 are rejected under 35 U.S.C. § 112, first paragraph, for "lack of enablement." The Office Action dated November 30, 2007, contends that "the specification, while being enabling for detecting methylation in DAPK and PR genes, does not reasonably provide enablement for characterizing cancer based upon methylation profiles for DAPK and PR." The Applicants respectfully traverse the rejection in view of the foregoing amendments, the Levenson Declaration, and the following reasons.

Claims 6-10 have been cancelled, obviating the rejection.

Claim 3, from which the remaining rejected claims depend, has been amended to recite a method of characterizing breast cancer in a subject that includes detecting the presence or absence of DNA methylation in a plurality of genes including DAPK. As amended, claim 3 does not recite "PR." The other independent claims in the application, claims 1 and 33, have been amended similarly. The Applicants respectfully contend that one skilled in the art, practicing the methods taught in the application, would be able to diagnose or characterize breast cancer in a subject. As support for this contention, the Applicants have provided a Declaration under 37 C.F.R. § 1.132, executed by inventor Dr. Victor V. Levenson, (hereinafter Levenson Declaration).

In his Declaration, Dr. Levenson describes experiments in which breast cancer was characterized in patients by detecting methylation in DAPK1 and additional genes that together were utilized as a composite "biomarker." In Dr. Levenson's Grant Proposal which accompanies his Declaration, results are presented from experiments in which plasma samples from twenty-nine (29)

normal patients or plasma samples from twenty-nine (29) patients with ductal carcinoma *in situ* (DCIS) were tested. (*See* Grant Proposal, page 4, Table 3 and accompanying text.) The methylation status of genes comprising a biomarker were assessed, including DAPK1 and additional genes. (*See id.*) Utilizing the methods disclosed in the present application, 89.3% of DCIS samples were found to exhibit methylation in the DAPK1 gene. (*See id.*) In contrast, 51.9% of normal samples were found to exhibit methylation in the DAPK gene. (*See id.*) This biomarker comprising DAPK1 and additional genes was shown to identify DCIS with 84% sensitivity and 80% specificity, utilizing the disclosed statistical procedures. (*See* Grant Proposal at page 4, Table 4 and at pages 7-8, under heading "Statistical analysis".)

In Dr. Levenson's Grant Proposal at page 4, Table 5, results are presented from experiments in which plasma samples from three (3) healthy patients or plasma samples from three (3) patients with atypical ductal hyperplasia (ADH) were tested. Utilizing the methods disclosed in the present application, the methylation status of DAPK1 was assessed and 37.5% of ADH samples were found to exhibit methylation in the DAPK1 gene. (*See id.*) None of the normal samples were found to exhibit methylation in the DAPK gene (0%). (*See* Grant Proposal, page 4, Table 5.) While this patient sample is small, it nonetheless demonstrates that methylation differences in the DAPK1 gene are observed for patients with ADH versus healthy patients and these results correlate with the results observed for the twenty-nine (29) patients with DCIS versus healthy patients.

For these reasons, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement, are requested. One skilled in the art clearly could practice the claimed methods for diagnosing or characterizing breast cancer in a patient utilizing the methylation of DAPK and additional genes as a biomarker.

VII. Conclusion

The Applicants have attempted in earnest to respond to the outstanding Office Action. Allowance of the pending claims is requested. If the Examiner believes that a conference will facilitate prosecution of the application, the Examiner is requested to contact Applicants' representative below.

Respectfully submitted,

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